FORUM

Making Sense of Our Metabolisms

Human nutrition research entered a new era in June 2000 when the full sequence of the human genome was published. Now, for the first time, nutrition scientists can determine why some people can eat all they want and never become obese, whereas others seem to gain weight just looking at food. Also, nutrition scientists can identify how individuals adjust to widely varying intakes of nutrients and remain healthy.

To address these issues, nutritionists need to conduct comprehensive studies of the effect of certain diet treatments on metabolism, physiological function, and health as well as the genetic response to those treatments. The six ARS Human Nutrition Research Centers provide a unique setting for investigators to explore some mystifying nutrition questions.

In her Food and Agricultural Policy Statement, USDA Secretary Ann M. Veneman identified the need to establish "outcome-based performance measures" for evaluating the impact of federal food assistance programs. This means that we need sensitive, precise markers of when dietary needs are met and when they are not. Such markers are not available for most nutrients. And today nutrition scientists have a whole new set of markers to test—markers of gene expression.

We've known for more than 150 years that organisms respond to dietary changes by changing their metabolism. Metabolic adjustments are presumably made by "sensors" responding to dietary changes in vitamin A, calcium, or selenium. These sensors have not yet been identified, so nutritionists measure aspects of metabolism that may have changed as a result of the action of the sensors. It is very difficult to detect the many metabolic adjustments that occur in the body after it's been disturbed by a change. It is likely that sensors are products of the human genome. In other words, certain genes are turned on or off either to produce or stop producing a protein that signals a whole cascade of metabolic events.

The story on page 4 of this issue describes zinc studies at the ARS Western Human Nutrition Research Center at Davis, California. Researchers there have identified mechanisms—proteins called zinc transporters—that control the uptake and release of zinc from cells. The scientists think that these proteins are sensors to changes in dietary zinc.

We have known for decades that individuals vary in the way they absorb and use essential nutrients. The human genome provides a tool for understanding these perplexing differences. The fact that no two people are alike stems from variations of single nucleotide bases in the double strand of DNA. These variations are called single polynuclear polymorphisms, or SNPs. Some SNPs can have serious effects on metabolism by altering the structure or function of enzymes or proteins.

More modest changes may explain variations in nutrient use. For example, a few years ago, scientists at the ARS Jean Mayer Human Nutrition Research Center on Aging at Tufts University in Boston, Massachusetts, and elsewhere reported that an SNP in the vitamin D receptor seemed to cause differences in bone mineral density of women. These reports have not been consistently confirmed, but they're tantalizing.

Studies of large populations show that some—but not all—individuals who eat less salt, five servings of fruits and vegetables per day, or less fat experience health benefits. This variation seems to reflect genetic differences. For example, ARS researchers found that people with the APOE4 genotype can successfully reduce their LDL cholesterol—the so-called bad kind—by simply changing what they eat. (See "Attacking Heart Disease at Its Genetic Base," *Agricultural Research,* July 1999, pp. 20–21.) Others without that genotype may not benefit at all.

At the Children's Nutrition Research Center at Baylor College of Medicine in Houston, Texas, researchers found that genes influence children's ability to absorb calcium, which may affect their later osteoporosis risk.

Davis researchers showed that when given the same amount of beta-carotene in their diets, some women converted considerably more to vitamin A than did others. (See "New Clues About Carotenes Revealed," *Agricultural Research,* March 2001, pp. 12–13.) And the story on page 8 of the current issue describes an ARS researcher's plans to measure variations in genetic response to selenium supplements. Such work may provide valuable clues as to why the risk of cancer is reduced in some individuals given supplemental selenium but not in others.

Scientists use a technique called quantitative trait locus, or QTL, to identify a set of genetic traits associated with increased risk for a disease or a biological characteristic. Nutritionists can use QTL to identify a set of genetic traits associated with changes in diet. QTL analysis will enable us to characterize individual variations in nutrient absorption, use, or requirements. This is the first step toward individualizing dietary recommendations. QTL analysis can also be used to compare the genetic response to a dietary intervention with the genetic patterns associated with a disease. If the intervention alters some of the same genes in the same way as occurs with hypertension, for example, that particular diet may be useful for reducing risk for that disease.

Linking diet and genomics requires incorporating new tools into human metabolic studies. Scientists from all the Centers will meet at Davis this month to establish protocols for these studies. The group will also develop a nutrition-genomic database that will allow full analysis of existing and future data. In this way, ARS human nutrition research will help define new, sensitive markers of nutritional health and of the variability in nutrient requirements and function. All of this work will strengthen the basis for food and nutrition policies and recommendations in the United States.

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